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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1652	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/459,573	LIVSHITS ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1(C)-(H), 4-6, 8-10, and 14-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7 and 11-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2-4,10,13*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 1-26 are pending in the application.

Receipt of an Information Disclosure Statement in Paper No. 13, filed 10/31/01 and applicants' election with traverse of Group I, claims 1(A)-(B), 2, 3, 7, and 11-13, drawn to an Escherichia bacterium expressing the polypeptide of SEQ ID NO:10 and having an ability to produce an L-amino acid in Paper No. 12, filed 10/05/01 are acknowledged.

Applicants traverse the restriction requirement on the grounds that a search of all claims would not constitute a serious burden of search on the Office, particularly in view of the fact that the Groups are classified in only two subclasses. Applicants' argument is not found persuasive. As stated in a previous Office action (Paper No. 11), "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP 808.02". Each of Groups I-IV are drawn to a bacterium expressing a distinct polypeptide sequence, each requiring a *separate search*. Furthermore, the bacteria listed as Groups I-IV (classified in class 435/252.33) and the methods of use thereof listed in Groups V-VIII (classified in class 435/106) have *different classifications*. Therefore, co-examination of the claims of Groups I-VIII would require a serious burden of search on the examiner.

Applicants further argue that if the product claims of elected Group I are found allowable, the process claims of Group V should be re-joined. However, as the elected claims are not yet allowable, rejoinder is not as yet required. Applicants are advised to amend process claims of Group V accordingly in anticipation of allowance of the product claims of Group I.

Claims 1 (C)-(H), 4-6, 8-10, and 14-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicants should note that claims 2, 3, 7, and 11-13 have further been examined only to the extent that they read on the elected invention.

Drawings

1. The drawings submitted with this application have not been reviewed by a draftsperson at this time. Upon allowance of claimed subject matter, the draftsperson will perform a review. Direct any inquiries concerning drawing review to the Drawing Review Branch (703) 305-8404.

Specification/Informalities

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "*Escherichia* Bacteria Overexpressing the *yahn* Gene for Feedback-Insensitive Amino Acid Production". See MPEP § 606.01.

Claim Objections

3. Claim 1 is objected to because of the following informalities: the term "in Sequence Listing" in claim 1 is grammatically incorrect and should be replaced with, for example, "in the Sequence Listing". Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 1-3, 7, and 11 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to a bacterium. As written, the claims read on a product of nature and should be amended to indicate the hand of the inventor, for example, by addition of the term "purified" or "isolated" to identify a product that is not found in nature. See MPEP § 2105.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-3, 7, and 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 2, 3, 7, and 11 (claims 12 and 13 dependent therefrom) are indefinite because the claims are dependent upon non-elected claims.

7. The term "increased" in claims 1 (claims 2, 3, 7, dependent therefrom) and 11 (claims 12 and 13 dependent therefrom) is unclear absent a statement defining to what the level of L-amino acid production (claim 1) or copy number (claim 11) is being compared. The term "increased" is a relative term and the claim should define and clearly state as to what the amino acid production or copy number is being compared (i.e., increased production or copy number in comparison to what level of production or copy number?).

8. The term "inversion" in claim 1 (B) is unclear and confusing. The term is not defined by the claim nor the specification and the meaning of this term is unclear. It is suggested that the term "inversion" be deleted.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, 7, and 11-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 (claims 2, 3, 7, 12, and 13 dependent therefrom) and 11 are directed to a genus of *Escherichia* bacteria with an increased level of the polypeptide of SEQ ID NO:10 or a deletion, substitution, insertion, or addition variant thereof with an ability to increase L-amino acid production (claim 1), and optionally wherein the a copy of the DNA encoding the protein in a cell is increased (claim 11). The specification teaches only a single representative species of such bacteria, i.e., *Escherichia* bacteria transformed with an expression vector comprising the polynucleotide of SEQ ID NO:9 and overexpressing the polypeptide of SEQ ID NO:10. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being *Escherichia* bacteria with enhanced L-amino acid production by increasing expression of the polypeptide of SEQ ID NO:10 or a deletion, substitution, insertion, or addition variant thereof with an ability to increase L-amino acid production, and optionally wherein the a copy of the DNA encoding the protein in a cell is increased. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

10. Claims 1-3, 7, and 11-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an Escherichia bacteria transformed with an expression vector comprising the polynucleotide of SEQ ID NO:9 for increased expression of the polypeptide of SEQ ID NO:10 for the increased production of L-glutamate, L-lysine, and L-proline, does not reasonably provide enablement for an Escherichia bacterium with increased expression of the polypeptide of SEQ ID NO:10 or *any* deletion, substitution, insertion, or addition variant thereof with an ability to increase *any* L-amino acid production, and optionally wherein the copy number of the DNA encoding the protein in a cell is increased. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1 (claims 7, 12, and 13 dependent therefrom) 2, 3, and 11 are so broad as to encompass an Escherichia bacterium with increased expression of the polypeptide of SEQ ID NO:10 or *any* deletion, substitution, insertion, or addition variant thereof with an ability to increase *any* L-amino acid production, and optionally wherein the copy number of the DNA encoding the protein in a cell is increased. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of bacteria, variants of the polypeptide of SEQ ID NO:10, and bacteria with increased DNA copy numbers broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to an Escherichia bacteria transformed with an expression vector comprising the polynucleotide of SEQ ID NO:9 for increased expression of the polypeptide of SEQ ID NO:10 for the increased production of L-glutamate, L-lysine, and L-proline.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to

modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass an Escherichia bacterium with increased expression of the polypeptide of SEQ ID NO:10 or *any* deletion, substitution, insertion, or addition variant thereof with an ability to increase *any* L-amino acid production, and optionally wherein the copy number of the DNA encoding the protein in a cell is increased because the specification does not establish: (A) methods for increasing copy number of a DNA encoding the polypeptide of SEQ ID NO:10 or variants thereof as encompassed by the claims other than by transforming a bacterium of the genus Escherichia with an expression vector comprising the nucleic acid of SEQ ID NO:9 expressing the polypeptide of SEQ ID NO:10; (B) regions of the polypeptide of SEQ ID NO:10 that may be modified without affecting activity; (C) the general tolerance of the polypeptide of SEQ ID NO:10 to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any residues of the polypeptide of SEQ ID NO:10 with an expectation of obtaining the desired biological function; (E) methods of using the claimed Escherichia bacteria for increased production of *any* L-amino acid – applicants have demonstrated in the specification at pages 27, 28, and 35 increased production of *only* glutamate, lysine, and proline, respectively by increased expression of the yahn gene and the expectation that overexpression of the yahn gene will enhance production of *any* L-amino acid is highly unpredictable; and (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including *any* bacterium of the genus Escherichia with increased expression of the polypeptide of SEQ ID NO:10 or *any* deletion, substitution, insertion, or addition variant thereof with an ability to increase L-amino acid production. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation

left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. Claims 1, 2, 11, and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,040,160 ('160). Claims 1, 2, 11, and 12 are drawn to an Escherichia bacterium having an ability to produce an L-amino acid, wherein L-amino acid production is increased by increasing expression of the polypeptide of SEQ ID NO:10 or deletion, substitution, insertion, addition variants thereof, wherein the variant has an activity that increases the production of the L-amino acid of the bacterium (claim 1), and optionally wherein the L-amino acid is L-lysine (claim 2), and optionally wherein the copy number for the DNA encoding said polyptide is increased (claim 11), and optionally wherein the DNA is carried on a multicopy vector (claim 12). '160 teaches an Escherichia bacterium transformed with a vector encoding aspartokinase III with mutations to inhibit feedback inhibition by lysine (abstract). This anticipates claims 1, 2, 11, and 12 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1, 2, and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blattner et al. (GenBank Accession Number P75693, 01 November 1997) in view of Vrljic et al. (Mol Microbiol 22:815-826), and '160. Claims 1, 2, and 11-13 are drawn to an Escherichia bacterium having an ability to produce an L-amino acid, wherein L-amino acid production is increased by increasing expression of the polypeptide of SEQ ID NO:10 or deletion, substitution, insertion, addition variants thereof, wherein the variant has an activity that increases the production of the L-amino acid of the bacterium (claim 1), and optionally wherein the L-amino acid is L-lysine (claim 2), and optionally wherein the copy number for the DNA encoding said polyptide is increased (claim 11), and optionally wherein the DNA is carried on a multicopy vector (claim 12) or a transposon (claim 13).

Blattner et al. teach a polypeptide, YAHN, and the encoding nucleic acid sequence, yahn, isolated from *Escherichia coli* K-12. The polypeptide of Blattner et al. is 100 % identical to the polypeptide of SEQ ID NO:10. Blattner et al. teach that the YAHN polypeptide is a transmembrane protein and that the YAHN polypeptide, based on sequence homology using the Pfam database, belongs to the LysE protein family. Blattner do not teach overexpression of the *yahn* gene for increased amino acid production.

Vrljic et al. teach the isolation of the Corynebacterium lysE gene (page 817) encoding the protein LysE. Vrljic et al. teach that LysE functions as a lysine transporter and overexpression of the lysE gene results in increased L-lysine export from the cell into the culture medium (page 819, Fig. 5).

'160 discloses the teachings as described above. In addition, '160 teaches that the bacterial strains Corynebactierium and Escherichia are used for the industrial production of L-lysine. '160 teaches disadvantages of expressing a Corynebacterial polypeptide in Escherichia by disclosing that expressing a Corynebacterial polypeptide in Escherichia requires a decreased cultivation temperature (thereby decreasing the growth rate) and results in proteolytic cleavage of the expressed polypeptide (column 1, lines 40-64). '160 recommends using a homologous gene for expression in E. coli in order to overcome such problems (column 1, line 65 – column 2, line 4).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Blattner et al., Vrljic et al., and '160 to insert the yahn gene into an expression vector or a transposon

and transform E. coli with said vector or transposon in order to overexpress YAHN and thereby increase E. coli L-lysine expression yields. One would have been motivated to transform E. coli with an expression vector or transposon comprising the yahn gene as taught by Blattner et al. in order to increase E. coli L-lysine expression yields because of the teachings of '160 for homologous gene expression as described above. One would have a reasonable expectation of success for transforming E. coli with an expression vector or transposon comprising the yahn gene as taught by Blattner et al. in order to increase E. coli L-lysine expression yields because of the results of Blattner et al. Therefore, claims 1, 2, and 11-13, drawn to a an Escherichia bacterium having an ability to produce an L-amino acid, wherein L-amino acid production is increased by increasing expression of the polypeptide of SEQ ID NO:10, and optionally wherein the L-amino acid is L-lysine, and optionally wherein the copy number for the DNA encoding said polyptide is increased, and optionally wherein the DNA is carried on a multicopy vector or a transposon would have been obvious to one of ordinary skill in the art.

Conclusion

13. No claim is in condition for allowance. All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 2:00 pm and from 3:30 pm to 5:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

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